Preemptive endoluminal vacuum therapy to reduce anastomotic leakage after esophagectomy: a game-changing approach?

Gubler, C ; Vetter, D ; Schmidt, H M ; Müller, P C ; Morell, B ; Raptis, D ; Gutschow, C A

Abstract: Endoluminal vacuum therapy (EVT) is an accepted treatment for anastomotic leakage (AL) after esophagectomy. A novel concept is to use this technology in a preemptive setting, with the aim to reduce the AL rate and postoperative morbidity. Preemptive EVT (pEVT) was performed intraoperatively in 19 consecutive patients undergoing minimally invasive esophagectomy, immediately after completion of esophagogastrostomy. Twelve patients (63%) were high-risk cases with severe comorbidity. The EVT device was removed routinely three to six (median 5) days after esophagectomy. The endpoints of this study were AL rate and postoperative morbidity. There were 20 anastomoses at risk in 19 patients. One patient (5.3%) experienced major morbidity (Clavien-Dindo grade IIIb) unrelated to anastomotic healing. He underwent open reanastomosis at postoperative day 12 with pEVT for redundancy of the gastric tube and failure of transition to oral diet. Mortality after 30 days was 0% and anastomotic healing was uneventful in 19/20 anastomoses (95%). One minor contained AL healed after a second course of EVT. Except early proximal dislodgement in one patient, there were no adverse events attributable to pEVT. The median comprehensive complication index 30 days after surgery was 20.9 (IQR 0-26.2). PEVT appears to be a safe procedure that may have the potential to improve surgical outcome in patients undergoing esophagectomy.

DOI: https://doi.org/10.1093/dote/doy126

Preemptive Endoluminal Vacuum Therapy after Esophagectomy: A Game-Changing Technology?

Christoph Gubler[2], Diana Vetter[1], Henner Schmidt[1], Philip C. Müller[1], Bernhard Morell[2], Dimitri Raptis[3] and Christian A. Gutschow[1]

[1]Department of Visceral and Transplant Surgery, University Hospital Zurich, Switzerland

[2]Department Gastroenterology, University Hospital Zurich, Switzerland

Correspondence Address:

Prof. Christian A. Gutschow

Division Head Upper Gastrointestinal Surgery

Department for Surgery and Transplantation

University Hospital Zurich

Rämistrasse 100

8091 Zurich

Switzerland

Phone: (+41) 044 255 9723

Mail: christian.gutschow@usz.ch

Conflicts of Interest:

The authors declare that they have no conflict of interest. The study was funded by institutional means.

Abstract (aktuell 175 words, max. 175 words)

Background:

Endoluminal vacuum therapy (EVT) is an accepted treatment for anastomotic leakage (AL) after esophagectomy. A new concept is to use this technology in a preemptive setting. The aim of this study was to assess the effect of preemptive EVT (PEVT) on postoperative morbidity.

Methods:

PEVT was performed in 13 patients undergoing minimally invasive esophagectomy. Indications for PEVT were high comorbidity or technical considerations during surgery. One patient underwent open re-anastomosis with PEVT for redundancy of the gastric tube at postoperative day 12. Endpoints of this study were postoperative morbidity and AL-rate.

Results:

Anastomotic healing was uneventful in 13/14 anastomoses (AL 7.1%). One minor AL healed after a second course of EVT. There were no adverse events attributable to PEVT. One patient experienced major morbidity (Clavien-Dindo grade IIIb) unrelated to anastomotic healing, and seven patients (54%) developed minor morbidity. The median comprehensive complication index 30 days after surgery was 20.9 (IQR 0-26.2).

Conclusions:

PEVT appears to be a safe procedure that may emerge as a groundbreaking technology in high-risk patients undergoing esophagectomy.

Introduction (Manuscript 1851 words, max. 1500 words)

Anastomotic leakage (AL) remains one of the most frequent complications after esophagectomy. It may be complicated by sepsis, multiple organ failure, and death [1,2]. The exact causes of AL are largely unknown; patients with severe comorbidities are at increased risk [3–5]. A current hypothesis is that the pathophysiology of AL is multifactorial and involves technical issues, local ischemia, bacterial superinfection, and inflammation [6,7].

Therapeutic strategies for AL have evolved dramatically, and interventional endoscopy has replaced surgical revision in most situations. In this context, endoluminal vacuum therapy (EVT) with a polyurethane foam has become an important therapeutic tool. EVT continuously removes secretions, improves interstitial edema and microcirculation, and induces granulation. Retrospective studies have shown excellent results and low complication rates [8,9].

A radically novel idea is to use the EVT technology to prevent AL. In a recent case series, early EVT in patients without leak, but with endoscopically proven anastomotic ischemia was effective in six of eight patients [10]. Likewise, intraoperative application of EVT to esophagogastric anastomoses with a 1cm defect resulted in complete healing in a live porcine model [11]. With this in mind and considering the high incidence and the deleterious effects of AL, we implemented *preemptive* EVT (PEVT) in patients undergoing esophagectomy and gastric tube reconstruction.

Patients and Methods

From a prospectively maintained database, we identified all patients that received PEVT during esophagectomy with esophago-gastrostomy between November 2017 and May 2018 at our department. Patient characteristics are displayed in Table 1. Institutional review board approval was obtained.

Records of patients were reviewed with respect to demographic characteristics, oncological parameters, surgical procedures, and the postoperative course up to 30 days after surgery. Endpoints of this study were postoperative morbidity and AL-rate, defined according to the Esophageal Complications Consensus Group (ECCG), the Clavien-Dindo (CD) classification, and the Comprehensive Complication Index (CCI).

PEVT was performed intraoperatively upon completion of esophago-gastrostomy. The surgical procedures were total (laparoscopic/thoracoscopic) minimally invasive Ivor Lewis esophagectomy (ttMIE) with high intrathoracic circular stapled end-to-side esophago-gastrostomy (n=12) and minimally invasive retrosternal gastric tube reconstruction with circular stapled end-to-side cervical esophago-gastrostomy in a patient undergoing secondary reconstruction after esophagectomy (n=1). One patient after ttMIE underwent re-thoracotomy and re-anastomosis with PEVT at postoperative day 12 for a redundant gastric tube that prohibited oral feeding.

The Eso-SPONGE® (B. Braun Melsungen AG, Melsungen, Germany) was positioned endoscopically via an overtube. The device consists of an open-pored polyurethane sponge fitted to a gastric tube. The central part of the sponge was placed exactly at the level of the anastomosis. The tube was then passed transnasally and connected to a vacuum pump (Medela Thopaz®, Medela Healthcare, Baar, Switzerland) that generated a continuous negative pressure of 75mmHg. The tube was marked and fixed at the level of the nostril to monitor and prevent dislocation. Prophylactic antibiosis (Tazobac®, Pfizer PFE GmbH, Zurich, Switzerland) was started intravenously for 5-7 days. Throughout therapy, the Eso-SPONGE® system was checked 6-hourly for leakage and dislocation. The sponge was removed after 4 to 6 days via gastroscopy. After removal, the anastomotic region was assessed endoscopically to

exclude leakage or ischemia, and the pylorus was evaluated for spasm. Repeat endoscopy, contrast radiography, or computed tomography to exclude AL were performed according to the further clinical course. Patient characteristics are expressed as mean (standard deviation) or median [interquartile range] for continuous variables and frequencies and percentages for categorical variables, respectively.

Results

Technical aspects of PEVT

There were no adverse events related to PEVT. In particular, there were no bleeding episodes, tracheobronchial fistulae, air leaks, disconnections or dislocations of the device. Endoscopic removal of the Eso-SPONGE® system was performed 5 (IQR 3-6) days after surgery without complications in all cases.

Anastomotic healing

Uneventful primary healing occurred in 13 of the 14 anastomoses (Figure 1) (AL rate 7.1%, stenosis rate 0%). In one patient after minimally invasive Ivor Lewis esophagectomy, a 2mm contained AL (ECCG type 2) was detected during endoscopic sponge removal (Figure 2a). This patient was an ASA III high-risk case with a Charlson-Comorbidity Index of 7 (insulin dependent DM II, history of coronary infarction and chronic kidney disease). Throughout the postoperative course, he remained asymptomatic without clinical signs of infection with unremarkable CRP levels and leukocyte counts. After a second stage of EVT over 5 days, the leak was closed (Figure 2b) with uneventful further clinical course until discharge 20 days after surgery.

Postoperative morbidity (Table 2)

There were no deaths in this series and none of the patients experienced morbidity > CD grade 3b. Postoperative intensive care unit and hospital stay was 1 (IQR 1-2) and 15 (IQR 11-16) days, respectively. Five patients (39%) had no postoperative complication, six patients developed one complication, and two patients experienced more than two complications. CD grade IIIb morbidity was the highest encountered in this study (n=1). This patient underwent revisional surgery at postoperative day 12 for redundancy of the gastric tube and failure of transition to oral diet. Open transthoracic revisional surgery was performed with shortening of the interponate, end-to-side re-anastomosis, and PEVD. The anastomotic healing of both the primary and revisional anastomosis was uneventful.

CD grade IIIa morbidity was experienced by three patients. In detail, one patient developed an ECCG type 2 AL, one patient a left pleural effusion that was treated with thoracic drainage, and one patient had a pyloric outlet obstruction requiring a single endoscopic dilation. The median CCI at 30 days after surgery was 20.9 (IQR 0-26.2). None of the patients displayed typical radiological signs of aspiration pneumonia.

Discussion

This is the first clinical series evaluating the effect of intraoperative PEVT on postoperative anastomotic healing and morbidity after esophagectomy. In contrast to other research [10], the Eso-SPONGE® device was placed during surgery, immediately after completion of the anastomosis. Clinical outcome in this series was excellent with zero mortality, no procedure-related adverse events, and very low postoperative morbidity.

AL may be subclassified into “contained” and “free” leaks [12]. In the contained situation, an extraluminal cavity is sealed by surrounding healthy tissue and conservative treatment is successful in 80-100%. In contrast, free AL may lead to gross contamination with the consequences of sepsis and death. Clinical experience shows that EVT has the potential to convert “free” into “contained” situations by creating a closed, granulating, and well-drained extraluminal cavity [9]. Although the exact mechanism is still unknown, recent research suggests that EVT promotes wound healing by increased anastomotic blood flow, modulation of cytokines and chemoreceptor-mediated cell signaling, leading to enhanced angiogenesis and deposition of granulation tissue[13].

The evidence published on PEVT in esophageal surgery is extremely limited. In a pilot study on domestic pigs undergoing Ivor Lewis esophagectomy [11], experimental anastomotic defects were treated with EVT (n=4) or received no specific treatment (control group, n=6). Three controls died within 24 hours and were excluded from analysis, whereas three controls surviving more than 24h showed frank AL and pleural contamination with gastric contents. In contrast, no leaks were detected

in the EVT group after a follow-up of 3-7 days (p=0.03) and the authors concluded that EVT may have the potential to close leaks that otherwise would not heal without surgical or endoscopic intervention.

A retrospective case-series investigated early postoperative EVT [10] in patients undergoing Ivor Lewis esophagectomy with endoscopically proven anastomotic ischemia. EVT led to complete mucosal recovery without AL in six of eight patients. Two patients developed small contained AL that were successfully treated by subsequent courses of EVT. No EVT-related adverse events were noted. The authors concluded that EVT may play an important role in the treatment of anastomotic ischemia following esophagectomy.

It is important to mention that both studies cited above have their focus on treatment of ischemia or AL, which represents a well-established indication for EVT. In contrast, the idea of our study was preemption; i.e. to promote primary anastomotic healing in a technically sound surgical situation that carries a high intrinsic risk for perioperative morbidity. Thus, to our best knowledge, this is the first clinical series investigating a truly preemptive use of EVT after esophagectomy in humans.

Undeniably, our study has some limitations. First, there are no accepted standards for ideal treatment duration and optimal negative system pressure. Therefore, those parameters had to be chosen empirically from our experience with EVT for anastomotic fistula. However, removal of the sponge was unproblematic and the negative pressure of -75mmHg was sufficient to promote formation of granulation tissue.

Another limitation may be the formation of anastomotic strictures, which is a well-described phenomenon after secondary healing of AL [14] and may be even more frequent after EVT treatment [15]. This may be a limiting factor for routine use of PEVT, as we cannot provide endoscopic long-term follow-up in our patients and are currently not able to exclude induction of stricture formation by PEVT. However, most patients treated in this series had uneventful transition to a normal diet. Another concern was that intraluminal placement of the sponge could promote aspiration of saliva. On the other hand, occlusion of the anastomotic area may also have a protective effect for aspiration

pneumonia, because the contents of the gastric tube are completely sealed off the supraglottic area. Either way, no aspiration was detected in our series.

Conclusion

PEVT appears to be a safe procedure that may reduce AL-related morbidity by promoting primary anastomotic healing and by sealing potential minor full-thickness defects at a very early stage to prevent free leakage in patients undergoing esophagectomy. PEVT may be particularly valuable in patients with relevant comorbidities and increased risk for AL. Therefore, the identification of subpopulations that will benefit most from PEVT should be the next step of clinical research in this field.

References

1 Seesing MFJ, Gisbertz SS, Goense L, van Hillegersberg R, Kroon HM, Lagarde SM, Ruurda JP, Slaman AE, van Berge Henegouwen MI, Wijnhoven BPL. A Propensity Score Matched Analysis of Open Versus Minimally Invasive Transthoracic Esophagectomy in the Netherlands. Ann Surg 2017; 266: 839–846

2 Schmidt HM, Gisbertz SS, Moons J, Rouvelas I, Kauppi J, Brown A, Asti E, Luyer M, Lagarde SM, Berlth F, Philippron A, Bruns C, Hölscher A, Schneider PM, Raptis DA, van Berge Henegouwen MI, Nafteux P, Nilsson M, Räsanen J, Palazzo F, Rosato E, Mercer S, Bonavina L, Nieuwenhuijzen G, Wijnhoven BPL, Schröder W, Pattyn P, Grimminger PP, Gutschow CA. Defining Benchmarks for Transthoracic Esophagectomy: A Multicenter Analysis of Total Minimally Invasive Esophagectomy in Low Risk Patients. Ann Surg 2017; 266: 814–821

3 Kassis ES, Kosinski AS, Ross P, Koppes KE, Donahue JM, Daniel VC. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. Ann Thorac Surg 2013; 96: 1919–1926

4 Raymond DP, Seder CW, Wright CD, Magee MJ, Kosinski AS, Cassivi SD, Grogan EL, Blackmon SH, Allen MS, Park BJ, Burfeind WR, Chang AC, DeCamp MM, Wormuth DW, Fernandez FG, Kozower BD. Predictors of Major Morbidity or Mortality After Resection for Esophageal Cancer: A Society of Thoracic Surgeons General Thoracic Surgery Database Risk Adjustment Model. Ann Thorac Surg 2016; 102: 207–214

5 Wright CD, Kucharczuk JC, O'Brien SM, Grab JD, Allen MS, Society of Thoracic Surgeons General Thoracic Surgery Database. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. J Thorac Cardiovasc Surg 2009; 137: 587–595; discussion 596

6 Bosmans JWAM, Jongen ACHM, Bouvy ND, Derikx JPM. Colorectal anastomotic healing: why the biological processes that lead to anastomotic leakage should be revealed prior to conducting intervention studies. BMC Gastroenterol 2015; 15: 180

7 Shogan BD, Belogortseva N, Luong PM, Zaborin A, Lax S, Bethel C, Ward M, Muldoon JP, Singer M, An G, Umanskiy K, Konda V, Shakhsheer B, Luo J, Klabbers R, Hancock LE, Gilbert J, Zaborina O, Alverdy JC. Collagen degradation and MMP9 activation by Enterococcus faecalis contribute to intestinal anastomotic leak. Sci Transl Med 2015; 7: 286ra68

8 Bludau M, Hölscher AH, Herbold T, Leers JM, Gutschow C, Fuchs H, Schröder W. Management of upper intestinal leaks using an endoscopic vacuum-assisted closure system (E-VAC). Surg Endosc 2014; 28: 896–901

9 Valli PV, Mertens JC, Kröger A, Gubler C, Gutschow C, Schneider PM, Bauerfeind P. Stent-over-sponge (SOS): a novel technique complementing endosponge therapy for foregut leaks and perforations. Endoscopy 2018; 50: 148–153

10 Neumann P-A, Mennigen R, Palmes D, Senninger N, Vowinkel T, Laukoetter MG. Pre-emptive endoscopic vacuum therapy for treatment of anastomotic ischemia after esophageal resections. Endoscopy 2017; 49: 498–503

11 Scott RB, Ritter LA, Shada AL, Feldman SH, Kleiner DE. Endoluminal Vacuum Therapy for Ivor Lewis Anastomotic Leaks: A Pilot Study in a Swine Model. Clin Transl Sci 2017; 10: 35–41

12 Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'Journo XB, Griffin SM, Hölscher AH, Hofstetter WL, Jobe BA, Kitagawa Y, Kucharczuk JC, Law SYK, Lerut TE, Maynard N, Pera M, Peters JH, Pramesh CS, Reynolds JV, Smithers BM, van Lanschot JJB. International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg 2015; 262: 286–294

13 Glass GE, Murphy GF, Esmaeili A, Lai L-M, Nanchahal J. Systematic review of molecular mechanism of action of negative-pressure wound therapy. Br J Surg 2014; 101: 1627–1636

14 Tanaka K, Makino T, Yamasaki M, Nishigaki T, Miyazaki Y, Takahashi T, Kurokawa Y, Nakajima K, Takiguchi S, Mori M, Doki Y. An analysis of the risk factors of anastomotic stricture after esophagectomy. Surg Today 2018; 48: 449–454

15 Heits N, Bernsmeier A, Reichert B, Hauser C, Hendricks A, Seifert D, Richter F, Schafmayer C, Ellrichmann M, Schniewind B, Hampe J, Becker T, Egberts J-H. Long-term quality of life after endovac-therapy in anastomotic leakages after esophagectomy. J Thorac Dis 2018; 10: 228–240

Figure legends

Figure 1: Example of an uneventful healing of the esophago-gastrostomy (arrow) after 5 days of preemptive endoluminal negative pressure therapy.

Figure 2: a. 2mm contained anastomotic leak (arrow) at initial diagnosis on postoperative day 5. **b.** The anastomotic leak (arrow) diminished after a second stage of endoluminal vacuum therapy for 5 more days.